REMARKS

I. Status of Claims

Claims 1-7, 9, 11 and 14 are pending in this application. Claims 4 and 14 are currently withdrawn. Claims 8, 10, 12-13, and 15 are canceled.

II. Claim Objections

The Examiner has objected to claim 4 as allegedly citing non-elected subject matter including SEQ ID NO: 2 and 3. Applicants respectfully traverse the objection and its supporting remarks.

Applicants have correctly designated claim 4 as withdrawn, reflecting the fact that it has not elected species. With the amendment filed 7/11/07, claim 4 now depends from claim 1. Therefore, Claim 1 is a generic linking claim that encompasses all three of SEQ ID NOs:2-4. Thus if Claim 1 is allowed, SEQ ID NOs: 2 and 3 (and therefore claim 4) could then be rejoined. Applicants therefore respectfully request that the Examiner withdraw the objection to claim 4.

III. Rejection under 35 U.S.C. § 112, first paragraph, enablement

Claims 1-3, 5-9, and 11 are rejected under 35 U.S.C. §112, first paragraph, as allegedly not reasonably providing enablement for any mutant *Neisseria meningitides* ADP-ribosylating protein or fragments thereof with any substitution at Glu-109 or Glu-111 or Glu-120.

Applicants respectfully traverse the rejection and its supporting remarks. As discussed in the previous response, applicants have enabled Glu to Asp substitutions at any of Glu-109, Glu-111 or Glu-120 by virtue of having generated and tested each. The specification on page 35, lines 25-30, indicates that these three residues were identified as catalytic residues based upon homology to other ADP-ribosylating enzymes. The experiments performed by the inventors and disclosed herein demonstrate that the homology is in fact correct and these three are necessary catalytic residues in this enzyme. One of skill in the art would understand that catalytic residues are surface exposed residue necessary for the enzyme to perform its catalytic activity. The applicants work

demonstrating that substitution of any one of these Glu residues with an Asp residue blocks catalytic activity while retaining or increasing the immunogenicity of the protein is extremely significant. Asp is very similar to Glu as it retains the negative charge of Glu while the side chain is only a single methyl group shorter. One of skill in the art would recognize that each of these three Glu residues are, as asserted by the inventors, three key residues in the catalysis performed by the enzyme. Since the catalytic residues are surface exposed, one of skill in the art would recognize that these three positions could each accommodate any of the other eighteen amino acid residues without significantly disturbing the fold of the enzyme and therefore maintaining the immunogenicity and adjuvant effect of the enzyme. One of skill in the art would further recognize that any of those eighteen other amino acid residues substituted at one of these three key catalytic residues would cause a similar or even greater reduction in the catalytic activity of the enzyme. If an Asp which has the same charge only almost the same size as Glu won't work, then certainly insertion of any other residue besides a Glu won't work either. Thus, one of skill in the art would recognize based upon the disclosure of the present application that any of the eighteen other residues substituted at one of the three locations would provide the claimed functions and therefore the inventors have enabled the claims.

Even if one of the skill in the art could not predict that any of the other eighteen other residues would provide the claimed function, screening such would be an entirely routine procedure using molecular biology and enzymology techniques well known in the art and as disclosed in the working example provided on pages 33 through 37 as applied to the Glu to Asp substitutions. All one of skill in the art would need to do is generate each of the eighteen substitutions at the three different positions and screen them for activity, which requires generating a mere fifty-seven mutants (3*18).

The Examiner has asserted that because the claimed invention is open-ended and would cover other mutations in the enzyme outside of the substitution mutations at the one of the three specified locations, the applicants have to enable one of skill in the art to make and use all of these other mutations in addition to enabling one of skill in the art to make and use the claimed substitution mutations. However, such other mutations are irrelevant to the scope of the claims

since their presence or absence do not affect whether the enzyme is within the scope of the claims – all that matters is whether there is a substitution at one of the three specified residues. Thus, the only question with regard to enablement is can one of skill in the art practice the claimed invention in whatever context they choose. The simple answer is yes. The claimed invention is a mutant enzyme which has reduced activity by virtue of mutation at one of the three catalytic residues. The claimed mutations can be introduced into any other context and will function as intended, i.e., the mutant enzyme will show reduced activity with the substitution mutation in at least one of the three claimed residues. It is highly unlikely if not impossible that one of skill in the art could be working on an enzyme with other mutations where introduction of the claimed mutations would not lead to an enzyme with reduced activity. Thus, the applicants have enabled the claimed invention reasonably commensurate with the claimed scope, i.e., one of skill in the art can use the invention as presently claimed.

Applicants therefore respectfully request that the Examiner withdraw the rejection of claims 1-3, 5-9 and 11 under U.S.C. §112, first paragraph, enablement.

IV. Rejection under 35 U.S.C. § 112, first paragraph, written description

Claims 1-3, 5-9, and 11 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

Applicants respectfully traverse the rejection and its supporting remarks. The Examiner has not established a prima facie case of failure to comply with the written description requirement. The specification must be taken as complying with the first paragraph of § 112 unless there is a reason to doubt the objective truth of the statements relied upon therein for enabling support (In re Marzocchi , 169 USPQ 367 (CCPA 1971)). The Examiner has not provided any reason to doubt that the specification fails to provide an adequate written description of the presently claimed invention. The only reference cited as support for the rejection is one case, *The Regents of the University of California v. Eli Lilly*, 119 F.3d 1559 (Fed. Cir. 1997). However, since compliance with the written description rejection is a fact-based inquiry, case law is only relevant to the issue to the extent the facts are similar. The ultimate question that must be asked is whether one of skill in

the art would recognize that the inventors were in possession of the claimed invention as of filing the patent application. In the present application, the claimed invention is to a mutant *Neisseria meningitidis* ADP-ribosylating enzyme with a substitution at one of three exactly specified locations in the enzyme. Those three locations are known to be the three catalytic residues from homology to other ADP-ribosylating enzymes and the mutational experiments set forth in the specification. In contrast, in *Eli Lilly*, the claims relate nucleic acids encoding insulin, in each case as functional proteins. Thus this case relate to the written description requirements for claiming a protein having a complex biological function where the protein is novel and therefore nothing is known about the protein, not to the written description requirements for claiming an enzyme which is mutated at one of three specified catalytic residues where the enzyme falls in a class of well known and well studies enzymes, which is much more predictable by virtue of all of the work done on homologous bacterial ADP ribosylating enzymes. Furthermore, since the written description requirement is evaluated as of the priority date of the patent, *Eli Lilly* is also irrelevant to establishing failure to comply with the written description requirement because the priority date for the patent at issue in *Eli Lilly* was June 9, 1977. The priority date on the present application is August 30, 2002, which is more than twenty-five years after the priority date of *Eli Lilly*. In the intervening twenty-five years, biochemistry and molecular biology has advanced by leaps and bounds, so what was unpredictable in 1977 is not necessarily still unpredictable in 2002 even ignoring the abundance of work done characterizing the structure and function of ADP-ribosylating enzymes as compared to the lack of such structural and functional characterization work done on insulin as of 1977.

The recent cases from the Federal Circuit, *Falkner v. Inglis*, 448 F.3d 1357, 79 USPQ2d 1001 (Fed. Cir. 2006) and *Capon v. Eshhar*, 418 F.3d 1349, 76 USPQ2d 1078 (Fed. Cir. 2005), are summarized in the MPEP in section 2163(a)(1). Both of these cases make clear that the case cited by the Examiner, *Eli Lilly*, only applies to new genes in entirely new functional classes. The present invention, however, is directed to very mutation at one of three exactly specified residues in a protein that is in a well characterized class of which is much like *Capon* which was claiming mutations that inactivated certain functions in viral proteins (without even specifying the exact residues to be mutated which makes the presently claimed invention more specific than that claimed in *Capon*).

As the Office Action makes a general allegation of unpredictability and cites an inapplicable case as the only support for this allegation, Applicants respectfully submit that the Examiner has failed to provide any reasons to doubt that one of ordinary skill would recognize that Applicants had possession of the invention at the time of filing of the application and has therefore failed to make a prima facie case for lack of written description.

There is sufficient written description

Even assuming that the Examiner has made a prima facie case for written description (which is traversed), the rejection is still successfully rebutted by the specification as filed in view of the state of the art at the time of filing.

The MPEP 2163(a)(1) makes clear that:

"'(1) examples are not necessary to support the adequacy of a written description requirement; (2) the written description standard may be met ... even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure.' *Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006). See also *Capon v. Eshhar*, 418 F.3d at 1358, 76 USPQ2d at 1084 ('The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes' where the genes were novel combinations of known DNA segments .')"

The MPEP 2163(a)(1) makes clear that, "[w]hat is conventional or well known to one of ordinary skill in the art need not be disclosed in detail." Citing to *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986). As the specification makes clear, the mutant enzyme is in a class of well characterized enzymes, ADP-ribosylating enzymes, and the three residues in which mutations are claimed are known to be involved in the enzyme catalysis.

Thus, the present invention is directed to an enzyme that has a mutation in one of three exactly specified residues. As discussed in the prior response and in the response to the enablement

rejection above, the inventors have demonstrated how important these residues are for this catalytic activity as replacement of any one of them with a very similar residue Asp reduces the activity as claimed. Thus, the relationship between the structure and function is completely clear. The inventors have demonstrated that the structural requirements for function (i.e., the catalytic activity) are Glu residues at those positions. Furthermore, since these three residues are catalytic residues at the surface of the molecule, the surface exposure would allow substitution of these three Glu with any of the other nineteen residues. Since the very similar Asp would not support the catalytic activity, one of skill in the art would recognize that the other eighteen residues would similarly not support the catalytic activity and therefore would structurally support the claimed function of reduced activity. Furthermore, as the catalytic residues are surface exposed, any of the other eighteen residues would be accommodated without altering the immunogenicity. Thus, one of skill in the art would recognize that the applicants had possession of the invention as presently claimed due to the exquisitely exacting structural requirements of a Glu residue at each of the three positions being required for function based upon the lack of function when substituted with the very similar Asp residue.

The Examiner's assertion that the fact that the claims are not limited to mutants that have mutations at only the three specified residues is irrelevant to determining the scope of the written description requirement. To satisfy the written description requirement, one must convey that the inventors were in possession of ***that which is claimed***. The Examiner is asserting that the applicants have not satisfied the written description requirement because of a failure to disclose elements that are not actually claimed but could be covered by virtue of the claims being open-ended comprising claims. The Examiner is correct that the claims, because they are open-ended, would cover mutant enzymes that have other mutations in addition to a substitution mutation at one of the three residues as claimed. However, these other mutations are not claim elements required for one to meet the claims. Further, if one of skill in the art makes a mutant enzyme with these hypothetical other mutations without making the claimed mutations that the inventors are clearly within possession of, that hypothetical mutant is not within the literal scope of the claims. But, if such a person of ordinary skill in the art decides to combine their hypothetical mutations with those that the inventors were in possession of, then the combined mutant would and fairly should be within the scope of the

claimed invention. As long as the inventors have described ***their*** invention sufficient to show possession of the ***claimed*** invention, it is irrelevant whether they have described every other thing that could be combined with their invention. Thus, applicants have met the written description requirement as they have demonstrated to one of skill in the art that they were in possession of the claimed invention.

Applicants therefore respectfully request that the Examiner withdraw the rejection of claims 1-3, 5-9 and 11 under U.S.C. §112, first paragraph, written description.

V. Rejection under 35 U.S.C. § 102

Claims 1-3, 5-9, and 11 are rejected under 35 U.S.C. §102(a) and (e) as allegedly being anticipated by Masignani *et al.* (WO 02/079242). Specifically, the Office Action alleges that Masignani *et al.* when given the broadest interpretation discloses the presently claimed invention.

Applicant respectfully traverses the rejection and its supporting remarks. 35 U.S.C. 102(e) applies when, "an application for patent, published under Section 122(b), ***by another*** filed in the United States ***before the invention by the applicant*** ... " After review, the applicants have confirmed that in light of the scope of the pending claims, that Rino Rappuoli is an inventor of the presently pending claims and has therefore been added by the petition submitted March 12, 2008. Therefore Masignani *et al.* is not available as 35 U.S.C. 102(e) prior art as Masignani is not a patent application "by another" since the inventors on the present application and Masignani *et al.* are now the same and all three inventors were obligated to assign their rights in the respective patent applications to the same inventors.

Furthermore, Masignani is not available under 35 U.S.C. 102(a) since, as noted by the Examiner, Masignani *et al.* published October 10, 2002. The date that a patent is available as 35 U.S.C. 102(a) art is the date that it is published as indicated in MPEP 2126.01 ("The date that the patent is made available to the public is the date it is available as a 35 U.S.C. 102(a) or (b) reference."). The present application has a priority date of August 30, 2002, which is before the publication of Masignani *et al.*

Applicants therefore respectfully request that the Examiner withdraw the rejection of claims 1-3, 5-9, and 11 under 35 U.S.C. 102(e) and (a) as Masignani *et al.* qualifies under neither statutory section.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 223002103000. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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